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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/765,668	01/27/2004	David B. Rozema	Mirus.042.02	9890

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EXAMINER	
DUNSTON, JENNIFER ANN	
ART UNIT	PAPER NUMBER
1636	
MAIL DATE	DELIVERY MODE
03/18/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/765,668	ROZEMA ET AL.	
	Examiner	Art Unit	
	JENNIFER DUNSTON	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 January 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *5,7,8,12,16,17,21 and 22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *5,7,8,12,16,17,21 and 22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *27 January 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 1/7/2009 has been entered.

No claim amendments were made in the reply filed 1/7/2009. Claims 5, 7, 8, 12, 16, 17, 21 and 22 are pending and under consideration.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 5, 7, 8 and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Adams et al (US Patent Application Publication No. 2005/0153926 A1, cited in a prior action; see the entire reference) in view of Heller et al (Journal of Applied Polymer Science, Vol. 22, pages 1991-2009, 1978; see the entire reference). This rejection was made in the Office action mailed 10/1/2008 and is reiterated below.

Adams et al teach a method of delivery a polynucleotide to the cytoplasm of a cell, consisting of (i) forming a composition comprising a water soluble polymer such as styrene-maleic anhydride, divinylether-maleic acid or poly(maleic anhydride-co-vinyl ether) and a nucleic acid linked to the polymer via an ethylene group (a functional group), where the polymer is further modified by reacting with hydrophobic alcohols or amines, and (ii) administering the composition to a cell *in vitro* such that the cell endocytoses the polymer and nucleic acid (e.g. paragraphs [0037], [0057], [0081]-[0084], [0090]-[0093], [0162] and [0171]). Adams et al teach that the ethylene functional group is a reactive group (e.g., paragraph [0013]).

Adams et al do not specifically teach that the water soluble styrene-maleic anhydride polymer, which is further modified by reacting with hydrophobic alcohols or amines, is a polyanion.

Heller et al teach that partially esterified copolymers derived from ethylene-maleic anhydride or methyl vinyl ether-maleic anhydride are readily prepared from commercially available alternating copolymers (e.g., page 1993, 1st full paragraph). Heller et al teach that the copolymers in the un-ionized state are hydrophobic and water insoluble, but in the ionized state they are water soluble (e.g., page 1993, 2nd full paragraph). The solubilization process is generically represented by Heller et al using the following formula on page 1993:

The copolymer comprises a solubilizing group –COOH and a hydrophobic group Y (e.g., page 1993, 3rd full paragraph). Heller et al teach that the hydrophobic group can be any hydrophobic group (e.g., page 1993, 3rd full paragraph).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the method of delivering a polynucleotide to the cytoplasm of a cell of Adams et al to include the addition of a single hydrophobic group to a maleic acid anhydride moiety as taught by Heller et al because Adams et al teach the reaction of the polymer with a hydrophobic alcohol or amine, and Heller et al it is within the ordinary skill in the art to use any hydrophobic group to react with the anhydride moiety.

One would have been motivated to make such a modification in order to receive the expected benefit of providing a water soluble polymer as taught by Heller et al. Adams et al teach the use of a water soluble polymer such as styrene-maleic anhydride further modified by reacting with hydrophobic alcohols or amines, and Heller et al teach that providing a carboxylic acid group and a hydrophobic group maintains water solubility. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent any evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

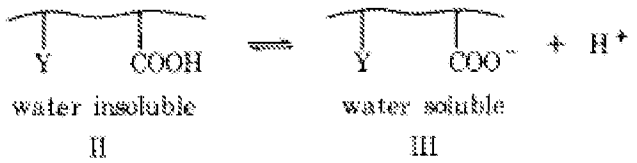
Claims 12, 16, 17 and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Adams et al (US Patent Application Publication No. 2005/0153926 A1, cited in a prior action; see the entire reference) in view of Heller et al (Journal of Applied Polymer Science, Vol. 22, pages 1991-2009, 1978; see the entire reference) and Tonge et al (US Patent No. 6,436,905, cited

in a prior action; see the entire reference). This rejection was made in the Office action mailed 10/1/2008 and is reiterated below.

Adams et al teach a method of delivery a polynucleotide to the cytoplasm of a cell, consisting of (i) forming a composition comprising a water soluble polymer such as styrene-maleic anhydride, divinylether-maleic acid or poly(maleic anhydride-co-vinyl ether) and a nucleic acid linked to the polymer via an ethylene group (a functional group), where the polymer is further modified by reacting with hydrophobic alcohols or amines, and (ii) administering the composition to a cell *in vitro* such that the cell endocytoses the polymer and nucleic acid (e.g. paragraphs [0037], [0057], [0081]-[0084], [0090]-[0093], [0162] and [0171]). Adams et al teach that the ethylene functional group is a reactive group (e.g., paragraph [0013]).

Adams et al do not specifically teach that the water soluble poly(maleic anhydride-co-vinyl ether) polymer, which is further modified by reacting with hydrophobic alcohols or amines, is a polyanion. Further, Adams et al do not specifically teach the poly(maleic anhydride-co-vinyl ether) polymer where the vinyl ether is butyl vinyl ether.

Heller et al teach that partially esterified copolymers derived from ethylene-maleic anhydride or methyl vinyl ether-maleic anhydride are readily prepared from commercially available alternating copolymers (e.g., page 1993, 1st full paragraph). Heller et al teach that the copolymers in the un-ionized state are hydrophobic and water insoluble, but in the ionized state they are water soluble (e.g., page 1993, 2nd full paragraph). The solubilization process is generically represented by Heller et al using the following formula on page 1993:



The copolymer comprises a solubilizing group –COOH and a hydrophobic group Y (e.g., page 1993, 3rd full paragraph). Heller et al teach that the hydrophobic group can be any hydrophobic group (e.g., page 1993, 3rd full paragraph).

Tonge et al teach a composition comprising a synthetic amphipathic polymer, including both hydrophobic groups and anionic hydrophilic groups and acting as a lipid-solubilizing agent (e.g. column 3, lines 49-52). Tonge et al teach that especially suitable polymers may be formed as alternating copolymers of maleic acid (or the anhydride thereof) with styrene, indene or a C_{1-4} alkyl, e.g. methyl substituted styrene or indene, or with propyl (or isopropyl) or butyl vinyl ether (e.g. column 6, lines 27-31, 60-63). Tonge et al disclose examples of suitable polymers, including Poly(maleic anhydride-styrene) (a random copolymer), Poly(maleic anhydride-propyl vinyl ether), and Poly(maleic anhydride-butyl vinyl ether) (e.g. column 6, lines 60-63). Tonge et al teach the use of the polymers to administer drugs or DNA or RNA to cells to facilitate the uptake of the therapeutic agent into target cells (e.g. column 1, lines 31-45; column 12, line 40 to column 13, line10).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the method of delivering a polynucleotide to the cytoplasm of a cell of Adams et al to include the addition of a single hydrophobic group to a maleic acid anhydride moiety as taught by Heller et al because Adams et al teach the reaction of the polymer with a hydrophobic alcohol or amine, and Heller et al it is within the ordinary skill in the art to use any

hydrophobic group to react with the anhydride moiety. Further, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the method of delivering a nucleic acid to a cell using a poly(maleic anhydride-co-vinyl ether)-based composition to include butyl vinyl ether as the vinyl ether, which is taught by Tonge et al, because Adams et al and Tonge et al teach it is within the ordinary skill in the art to use poly(maleic anhydride-co-vinyl ether)-based compositions for the delivery of nucleic acid to a cell.

One would have been motivated to make such a modification in order to receive the expected benefit of providing a water soluble polymer as taught by Heller et al. Adams et al teach the use of a water soluble polymer such as poly(maleic anhydride-co-vinyl ether) further modified by reacting with hydrophobic alcohols or amines, and Heller et al teach that providing a carboxylic acid group and a hydrophobic group maintains water solubility. Further, one would have been motivated to make such a modification in order to receive the expected benefit of defining the complete structure of the poly(maleic anhydride-co-vinyl ether) with a vinyl ether suitable for the delivery of nucleic acid as taught by Tonge et al. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent any evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Response to Arguments - 35 USC § 103

With respect to the rejection of claims 5, 7, 8 and 21 under 35 U.S.C. 103(a) as being unpatentable over Adams et al in view of Heller et al and the rejection of claims 12, 16, 17 and

22 under 35 U.S.C. 103(a) as being unpatentable over Adams et al in view of Heller et al and Tonge et al, Applicant's arguments filed 1/7/2009 have been fully considered but they are not persuasive.

The response asserts that the knowledge of Adams et al, when combined with Heller et al, would not be reasonably expected to lead one to the polymers described and claimed in the instant application. The response notes that the primary teaching of Adams et al is a nucleic acid with an ethylene-containing moiety which can be covalently or non-covalently linked to a polymer as a means of delivering the nucleic acid to a cell *in vivo* or *ex vivo*. This comment is not persuasive in overcoming the rejections of record, because a reference is prior art for all that it teaches.

The response notes that Adams et al teach that the polymers of the invention can have substantially any structure achievable by using subunits having a polymerizable or otherwise reactive ethylene moiety. This argument is not persuasive in overcoming the rejections of record, because Adams et al teach that preferred polymers containing anhydride groups, such as derivatives of maleic anhydride, including styrene-maleic anhydride and vinyl ether maleic anhydride copolymers (e.g., paragraph [0081]-[0083]).

The response cites paragraphs [0042], [0045] and [0050]-[0052] of Adams et al for teaching linkers and groups that would not be expected to motivate one skilled in the art of the desirability of a membrane active polyanion. These portions of Adams et al are directed to linkers for the addition of the nucleic acid molecule, which allow cleavage of the nucleic acid molecule from the polymer inside the cell. These are not the modifications of the maleic

anhydride moiety that are relied upon in the rejections of record. At paragraph [0057], Adams et al state the following:

> In another embodiment, the physicochemical characteristics (e.g., hydrophobicity, hydrophilicity, surface activity, conformation) of the polymer are altered by attaching a **monovalent moiety** which is different in composition than the constituents of the bulk polymer and which does not bear a nucleic acid. As used herein, "monovalent moiety" refers to organic molecules with only one reactive functional group. This functional group attaches the molecule to the polymer backbone. **"Monovalent moieties" are to be contrasted with the bifunctional linking groups described above**. Such monovalent groups are used to modify the hydrophilicity, hydrophobicity, binding characteristics, etc. of the polymer. Examples of groups useful for this purpose include long chain alcohols, amines, fatty acids, fatty acid derivatives, poly(ethyleneglycol) monomethyl ethers, etc. (emphasis added)

As stated by Adams et al, the monovalent moieties reacted with the polymer are distinct from the bifunctional linking groups described in paragraphs [0042], [0045] and [0050]-[0052].

The response asserts that paragraph [0057] of Adams et al teaches every conceivable modification without limit and does not teach or provide motivation for any particular desirable physiochemical characteristic. Further, the response asserts that Adams et al only teach the attachment of a single moiety and not a plurality of hydrophobic amines or alcohols as claimed. Even if Adams et al teach the addition of a single hydrophobic amine or alcohol, the rejections are based upon the combined teachings of Adams et al and Heller et al. Heller et al teach the addition of multiple hydrophobic groups to the anhydride of the polymer in order to provide water-solubility, which is a desirable feature taught by Adams et al (e.g., Abstract). In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

The response notes that Adams et al teach that exemplary copolymers include styrene-maleic anhydride, and other exemplary framework components include poly(maleic anhydride co-vinyl ether) and poly(styrene-maleic) anhydride. However, the response asserts that it is "readily known by those skilled in the art that these classes of polymers encompass polymers with a wide range of physiochemical characteristics and that not all poly(maleic anhydride-co-vinyl-ether) and poly(styrene-maleic anhydride) polymers are membrane active." Further, the response asserts that Applicant's claims do not encompass any and all poly(maleic anhydride-co-vinyl ether) polymers or poly(styrene-maleic anhydride) polymers, but are limited to a specific subset of polymers with a very specific physiochemical characteristic that is readily determined: capability of lysing mammalian cell membranes at pH 6.5. The arguments of counsel cannot take the place of evidence in the record. *In re Schulze*, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965); *In re Geisler*, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997). Applicant has not provided evidence that the poly(styrene-maleic anhydride) or butyl vinyl ether maleic anhydride copolymer substituted with the hydrophobic groups of Heller et al (2-12 carbons) would not be membrane active. Neither the response nor specification provides a "specific subset of polymers" that falls within the genus claimed and have the claimed function. The specification and claims disclose the structures generically, and all specific embodiments tested in the present specification are capable of lysing membranes at pH 6.5. Where the claimed and prior art products are identical or substantially identical, or are produced by identical or substantially identical processes, the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of the claimed product. See *In re Ludtke* 441 F.2d 660, 169 USPQ 563 (CCPA 1971). Whether the rejection is based on

"inherency" under 35 U.S.C. 102, or "prima facie obviousness" under 35 U.S.C. 103, jointly or alternatively, the burden of proof is the same, and its fairness is evidenced by the PTO's inability to manufacture products or to obtain and compare prior art products. *In re Best, Bolton, and Shaw*, 195 USPQ 430, 433 (CCPA 1977) citing *In re Brown*, 59 CCPA 1036, 459 F.2d 531, 173 USPQ 685 (1972). In the instant case, the references teach polymers that meet the structural limitations of the claims and would necessarily be capable of lysing membranes at pH 6.5. Applicant has not provided evidence that the prior art polymers are not capable of lysing membranes at pH 6.5.

The response asserts that Adams et al only teach the usefulness of polycations for membrane disruption at paragraph [0136]. As discussed above, the structures taught by the prior art meet the structural limitations of the claims, and would necessarily be capable of lysing membranes at pH 6.5. At paragraph [0136], Adams et al teach that the lipophilic long chain alkyl group of the compound is the endosome membrane disruption promoting component, and not the polylysine *per se*. Thus, the modification of the maleic anhydride based copolymers with a lipophilic long chain alkyl group (e.g., the long chain alcohols or amines of paragraph [0057] of Adams et al or the alcohols of Heller et al, as disclosed in the last paragraph of page 1993 and Table I), based upon the combined teachings of Adams et al and Heller et al, would be expected to result in membrane activity of the modified polymer.

The response asserts that Adams et al do not provide a suggestion or motivation for modified styrene-maleic anhydride random copolymers and ether-maleic anhydride alternating copolymers capable of lysing mammalian cell membranes at pH 6.5, one would not have been motivated to combine the synthetic method taught by Heller et al to generate Applicant's claimed

membrane active polymers and method. The fact that applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985). In the instant case, the motivation to combine the teachings of Adams et al and Heller et al is based upon achieving water-solubility of the polymer.

For these reasons, and the reasons made of record in the previous office actions, the rejections are maintained.

Conclusion

No claims are allowed.

All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period

will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Dunston whose telephone number is 571-272-2916. The examiner can normally be reached on M-F, 9 am to 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached at 571-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Jennifer Dunston, Ph.D.
Examiner
Art Unit 1636

/JD/

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